

What is claimed is:

1. A method for identifying genes responsible for high titer antibody production comprising:
 - (a) inactivating mismatch repair of said antibody-producing cells, thereby forming hypermutable cells,
 - (b) screening said hypermutable cells for cells that produce higher titers of antibody as compared to said antibody-producing cells, and
 - (c) analyzing the genomes of said antibody-producing cells and said hypermutable cells, thereby identifying genes responsible for high titer antibody production.
2. The method of claim 1 wherein said antibody-producing cell produces intact antibodies.
3. The method of claim 1 wherein said antibody-producing cell comprises endogenous immunoglobulin genes.
4. The method of claim 1 wherein said antibody-producing cell comprises exogenous immunoglobulin genes.
5. The method of claim 1 wherein said antibody-producing cell produces derivatives of immunoglobulin genes.
6. The method of claim 1 wherein said step of inactivating mismatch repair comprises introducing into said antibody-producing cells a dominant negative allele of a mismatch repair gene.
7. The method of claim 1 wherein said step of inactivating mismatch repair comprises knocking out at least one mismatch repair gene of said antibody-producing cells.
8. The method of claim 1 wherein said step of inactivating mismatch repair comprises introducing an RNA interference molecule into said antibody-producing cells.
9. The method of claim 1 wherein said step of inactivating mismatch repair comprises introducing an antisense molecule against a mismatch repair gene into said antibody-producing cells.
10. The method of claim 6 wherein said allele comprises a truncation mutation.
11. The method of claim 1 wherein the step of screening comprises analyzing a nucleotide sequence of the genome of said cells as compared to the genome of untreated cells.
12. The method of claim 1 wherein the step of screening comprises analyzing mRNA expression levels and structure from said cell as compared to untreated cells.
13. The method of claim 1 wherein the step of testing comprises analyzing protein from the said cell as compared to untreated cells.

14. The method of claim 1 wherein the step of screening comprises analyzing the phenotype of said gene.
15. The method of claim 1 wherein said antibody-producing cell is a mismatch repair defective fertilized egg of a non-human animal.
16. The method of claim 15 further comprising the step of implanting said fertilized egg into a pseudo-pregnant female, whereby said fertilized egg develops into a mature transgenic animal.
17. A homogeneous culture of high titer antibody producing cells produced by a method comprising the steps of:
 - (a) inactivating mismatch repair of said antibody-producing cells, thereby forming hypermutable cells;
 - (b) screening said hypermutable cells for cells that produce higher titers of antibody as compared to said antibody-producing cells;
 - (c) culturing said hypermutable cells producing higher titers of antibody.
18. The culture of high titer antibody producing cells of claim 17 wherein the high titer antibody-producing cell is selected from the group consisting of a bacterial cell, a yeast cell, a plant cell, a mammalian cell, a mouse cell, a rat cell, a rabbit cell, a hamster cell, and a non-human primate cell.
19. A method for producing a high titer antibody producing cell comprising the step of modulating the expression of at least one gene involved in antibody production wherein said genes comprise alpha 1-anti-trypsin and endothelial monocyte-activating polypeptide I.
20. The method of claim 19 wherein the cell is a hybridoma.
21. The method of claim 19 where in the cell is an epithelial cell.
22. The method of claim 19 where in the cell is ovarian.
23. The method of claim 19 where in the cell is a kidney cell.
24. The method of claim 19 where in the cell is a myeloid cell.
25. The method of claim 19 where in the cell is a lymphoid cell.
26. The method of claim 19 whereby said step of modulating comprises suppression of the expression of said genes by introducing an antisense oligonucleotide directed against at least one of said endothelial monocyte-activating polypeptide I and alpha-1-anti-trypsin genes.
27. The method of claim 19 whereby said step of modulating comprises suppression of the expression of said genes by introducing an expression vector comprising an antisense

- transcript directed against at least one of said endothelial monocyte-activating polypeptide I and alpha-1-anti-trypsin genes.
28. The method of claim 19 whereby said step of modulating comprises suppression of the expression of said genes by introducing a knock out targeting vector to disrupt the endogenous function of at least one of said endothelial monocyte-activating polypeptide I and alpha-1-anti-trypsin genes.
29. The method of claim 19 whereby said step of modulating comprises suppression of the expression of said genes by introducing a polynucleotide comprising a ribozyme directed against at least one of said endothelial monocyte-activating polypeptide I and alpha-1-anti-trypsin genes.
30. The method of claim 19 whereby suppression is achieved by introducing intracellular blocking antibodies against the product of said endothelial monocyte-activating polypeptide I and/or the alpha-1-anti-trypsin gene.
31. The method of claim 29 whereby suppression is achieved by incubating cells with neutralizing antibody or derivatives thereof directed against the product of said genes in the growth medium.
32. A method of modulating antibody production of cells comprising contacting said cells with protease inhibitors to decrease antibody production from antibody producer cells.
33. The method of claim 59 where the inhibitor comprises pharmacological amounts of natural protease substrates.
34. The method of claim 59 where said inhibitor is a blocking antibody to natural protease inhibitors.
35. The method of claim 59 where the inhibitor is a blocking antibody to alpha-1-anti-trypsin.
36. A method for selecting cells for high titer antibody production whereby growth medium of cells is analyzed for alpha-1-antitrypsin, where low levels are associated with high antibody titers.
37. The method of claim 36 wherein alpha-1-antitrypsin RNA, wherein low levels of RNA is associated with high antibody titers.
38. The method of claim 36 wherein alpha-1-antitrypsin protein, wherein low levels of RNA is associated with high antibody titers.
39. A method for selecting for cells for high titer antibody production whereby growth medium of cells is analyzed for endothelial monocyte-activating polypeptide I, where low levels are associated with high antibody titers.

40. The method of claim 39 wherein endothelial monocyte-activating polypeptide I RNA, wherein low levels of RNA is associated with high antibody titers.
41. The method of claim 39 wherein endothelial monocyte-activating polypeptide I protein, wherein low levels of RNA is associated with high antibody titers.
42. A method for suppressing antibody production associated with hyperimmunoglobulin disease production comprising contacting said cells with at least one compound that increases endothelial monocyte-activating polypeptide I expression.
43. A method for suppressing antibody production associated with hyperimmunoglobulin disease production comprising contacting said cells with at least one compound that increases alpha-1-antitrypsin expression.
44. A method for enhancing antibody production associated with hyporimmunoglobulin disease production comprising contacting said cells with at least one compound that suppresses alpha-1-anti-trypsin expression activity.
45. The method of claim 44 wherein said compound decreases the activity of alpha-1-antitrypsin protein in said cells.
46. The method of claim 44 wherein said compound decreases the level of alpha-1-antitrypsin in said cells.
47. A method for enhancing antibody production associated with hyporimmunoglobulin disease production comprising contacting said cells with at least one compound that suppresses monocyte-activating polypeptide I expression activity.
48. The method of claim 47 wherein said compound decreases the activity of monocyte-activating polypeptide I protein in said cells.
49. The method of claim 47 wherein said compound decreases the level of monocyte-activating polypeptide I in said cells.
50. A host cell for the expression of antibody molecules or fragments thereof comprising a defect in the monocyte-activating polypeptide I gene such that expression of monocyte-activating polypeptide I is inhibited.
51. The host cell of claim 50 wherein said defect comprises a deletion of the monocyte-activating polypeptide I.
52. The host cell of claim 50 wherein said defect is a frameshift mutation in the monocyte-activating polypeptide I gene.
53. The host cell of claim 50 wherein said host cell comprises an expression vector comprising an antisense transcript of the monocyte-activating polypeptide I gene

- whereby expression of said antisense transcript suppresses the expression of the monocyte-activating polypeptide I gene.
54. The host cell of claim 50 wherein said host cell comprises a ribozyme that disrupts expression of the monocyte-activating polypeptide I gene.
 55. The host cell of claim 50 wherein said host cell comprises an intracellular neutralizing antibody against the monocyte-activating polypeptide I protein whereby said antibody suppresses the activity of monocyte-activating polypeptide I.
 56. A host cell for the expression of antibody molecules or fragments thereof comprising a defect in the alpha-1-antitrypsin gene such that expression of alpha-1-antitrypsin is inhibited.
 57. The host cell of claim 56 wherein said defect comprises a deletion of the alpha-1-antitrypsin.
 58. The host cell of claim 56 wherein said defect is a frameshift mutation in the alpha-1-antitrypsin gene.
 59. The host cell of claim 56 wherein said host cell comprises an expression vector comprising an antisense transcript of the alpha-1-antitrypsin gene whereby expression of said antisense transcript suppresses the expression of the alpha-1-antitrypsin gene.
 60. The host cell of claim 56 wherein said host cell comprises a ribozyme that disrupts expression of the alpha-1-antitrypsin gene.
 61. The host cell of claim 56 wherein said host cell comprises an intracellular neutralizing antibody against the alpha-1-antitrypsin protein whereby said antibody suppresses the activity of alpha-1-antitrypsin.
 62. The host cell of claim 61 further comprising an expression vector comprising a polynucleotide sequence encoding at least a portion of an antibody molecule.
 63. The host cell of claim 61 wherein said polynucleotide encodes at least an immunoglobulin light chain or fragment thereof.
 64. The host cell of claim 61 wherein said polynucleotide encodes at least an immunoglobulin heavy chain or fragment thereof.
 65. The method of claim 1 further comprising the step of restabilizing the genome of selected high titer antibody-producing cells.
 66. A culture of stable, high titer antibody-producing cells made by the method of claim 65.